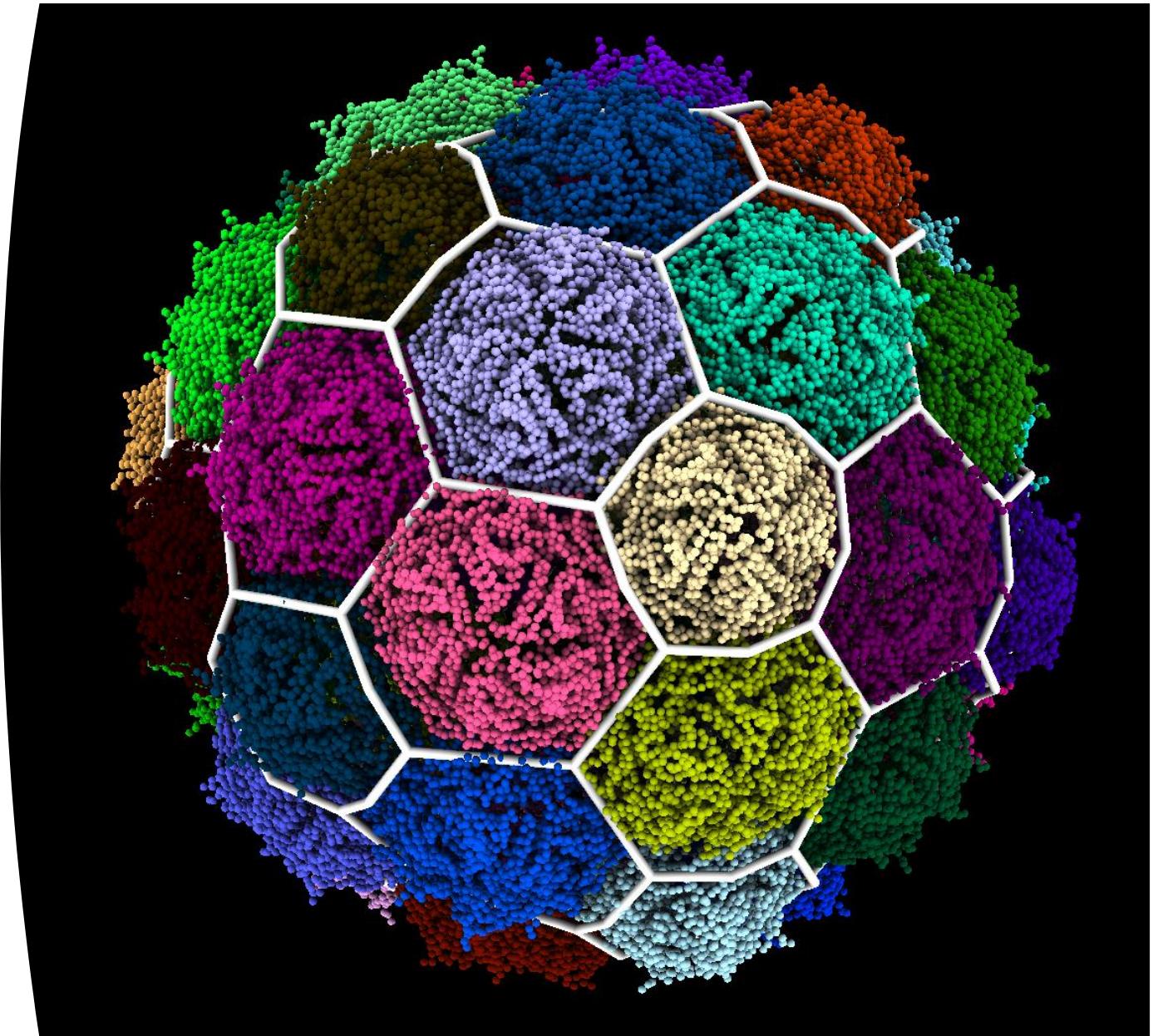
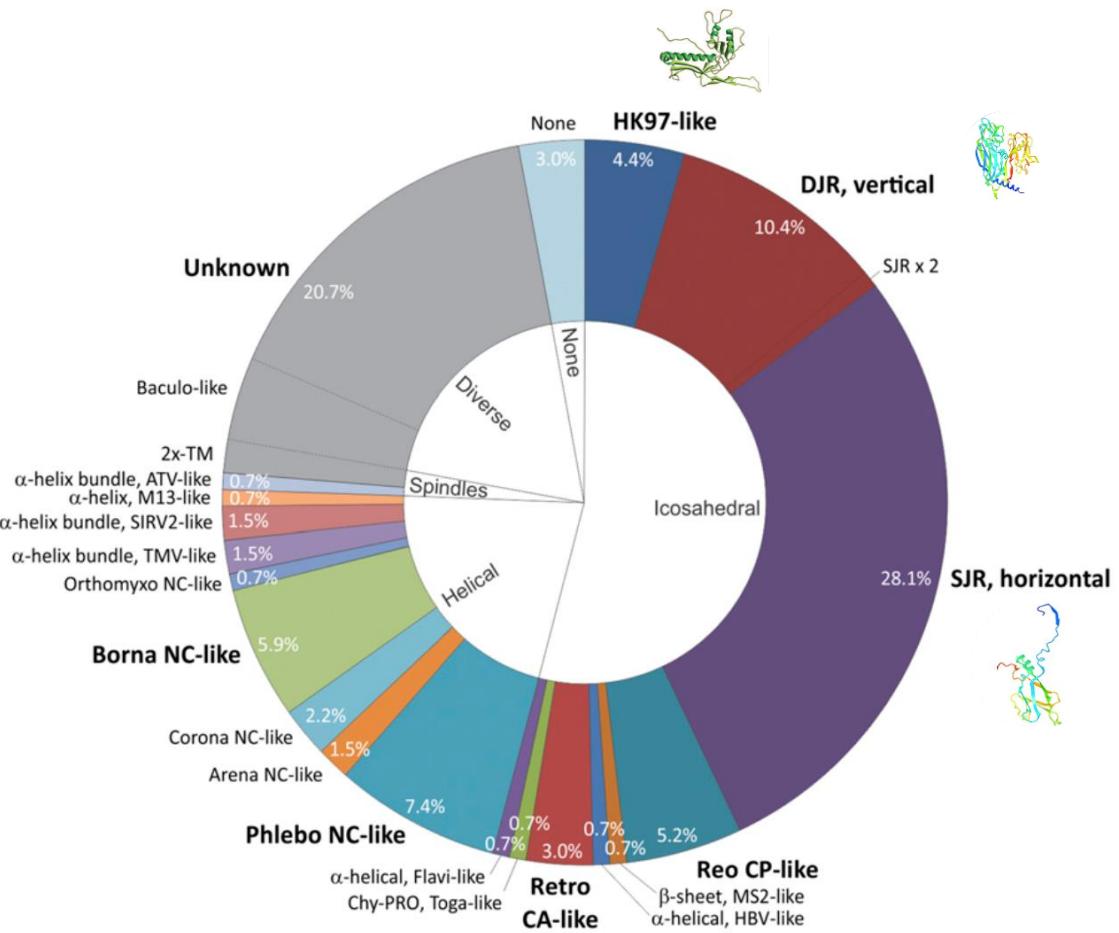


Structural Analysis & Classification Of HK97-like Viral Capsids

Colin Brown – MS Physics
Luque Lab



Icosahedral capsids dominate the virosphere



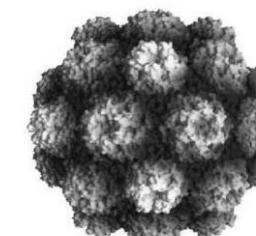
Krupovic and Koonin, PNAS 2017

Viral Capsids

- Contain the viral genome
- Built from repeated units

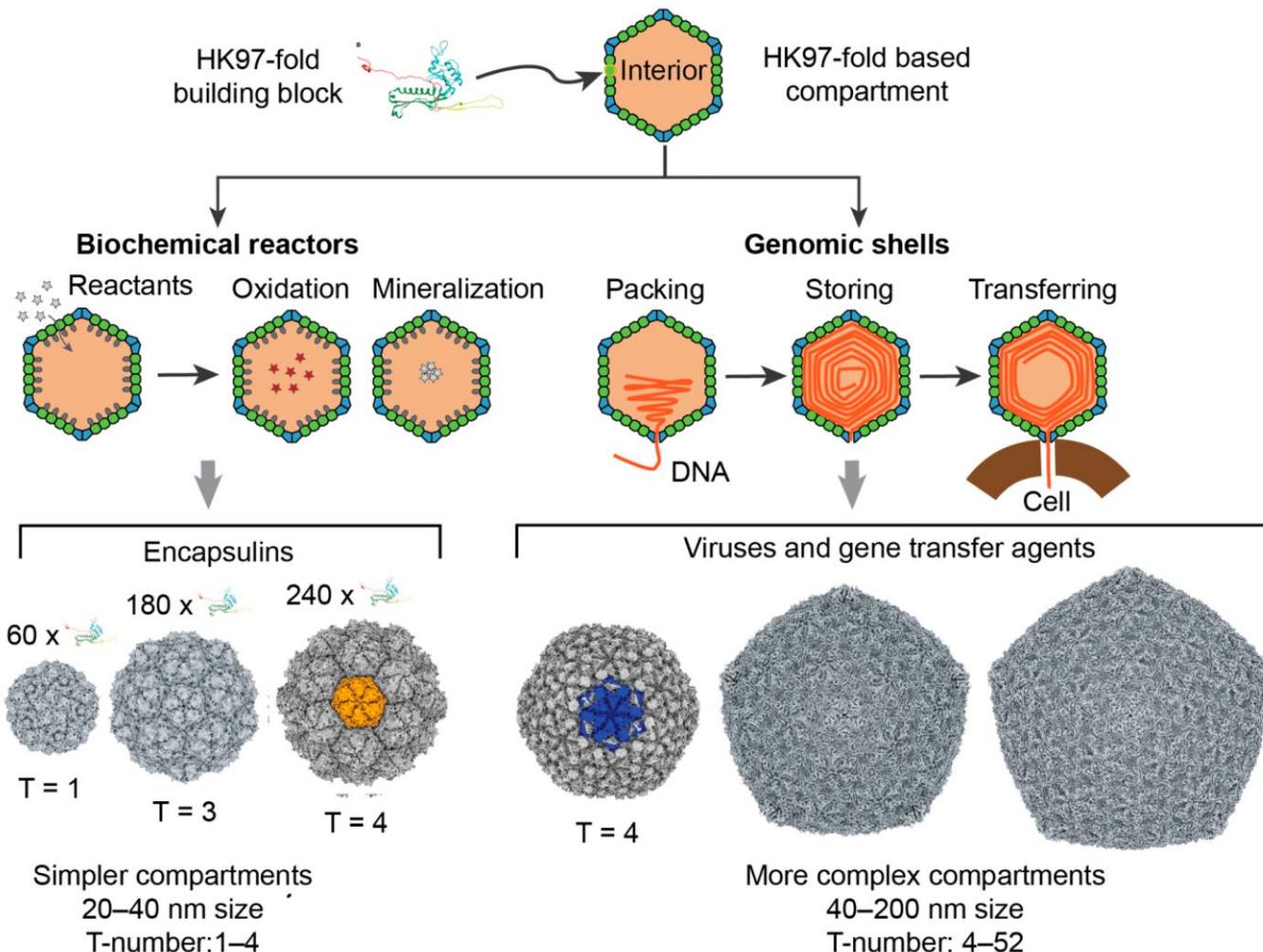
Icosahedral Capsids

- Highly symmetric
- >90% of viruses

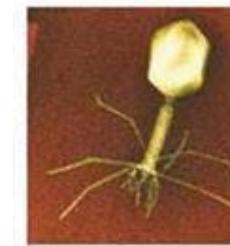


ICTVdB

HK97-Like Folds



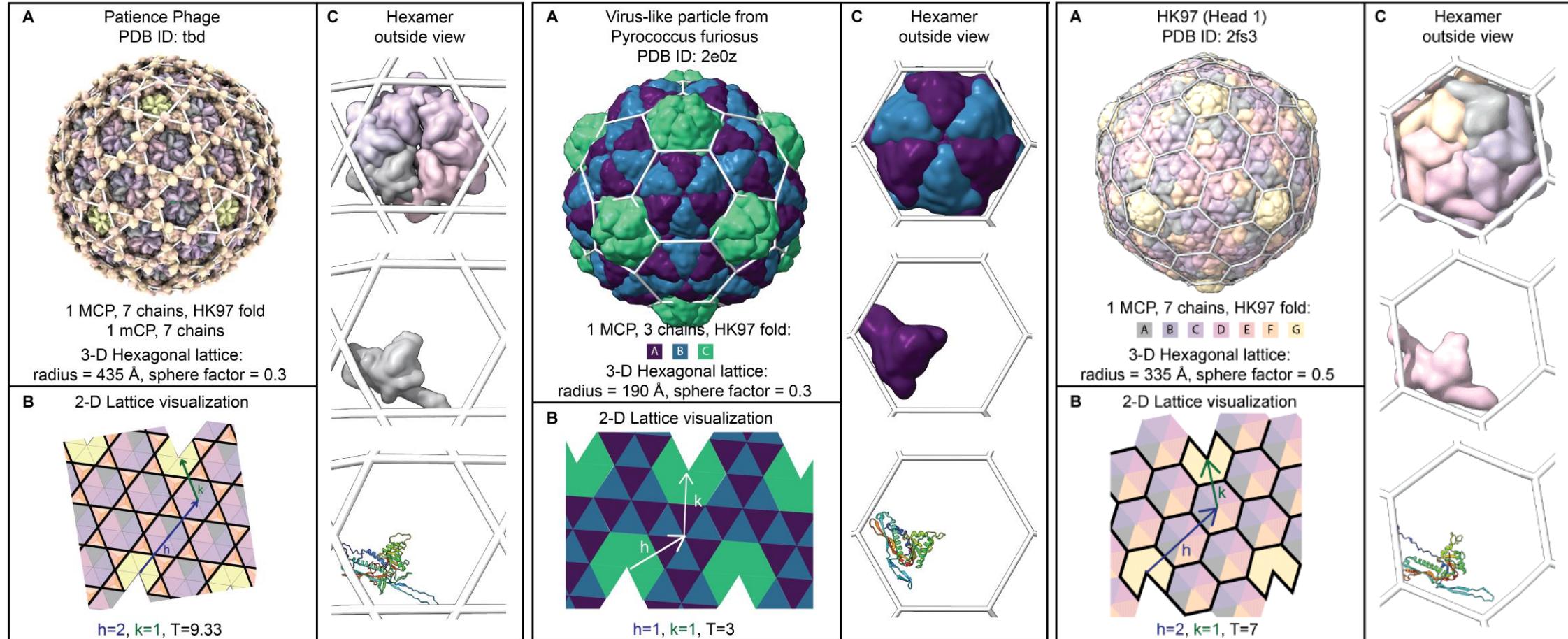
HK97-fold



Tailed bacteriophages

50%-90% of viral particles in the environment

Icosahedral Capsid Anatomy

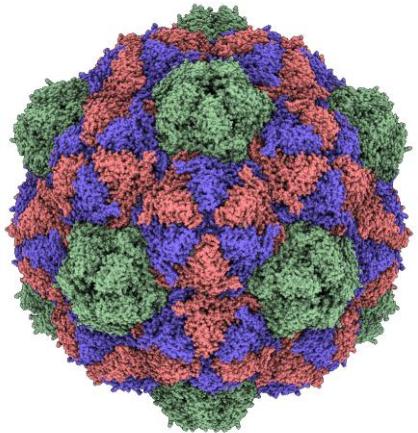


Lee, Brown, Bartels et al. In Preparation

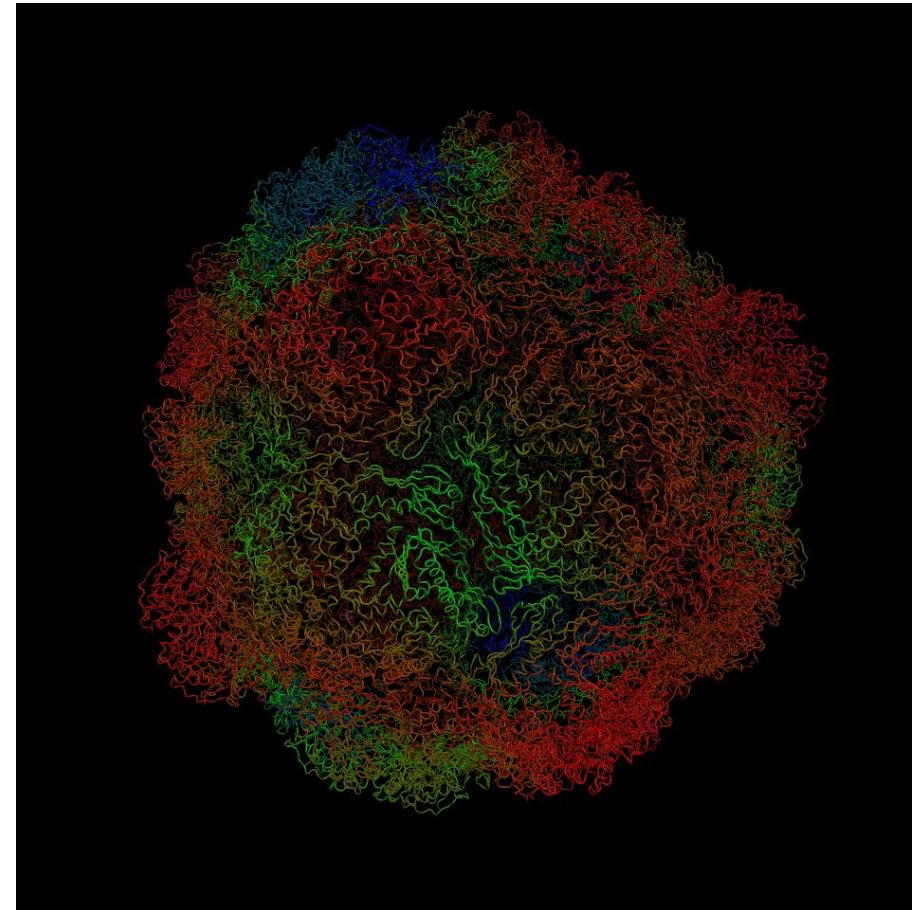
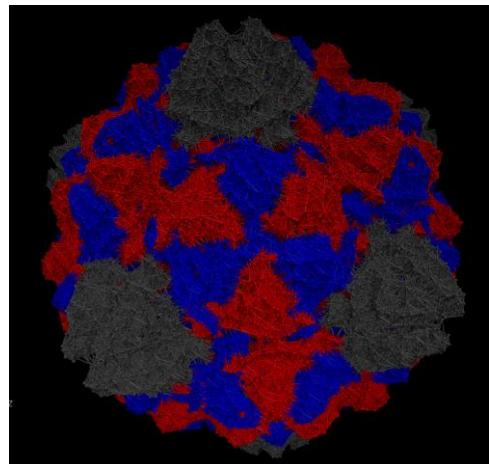
Step 1: Physical Model

Normal Mode Analysis

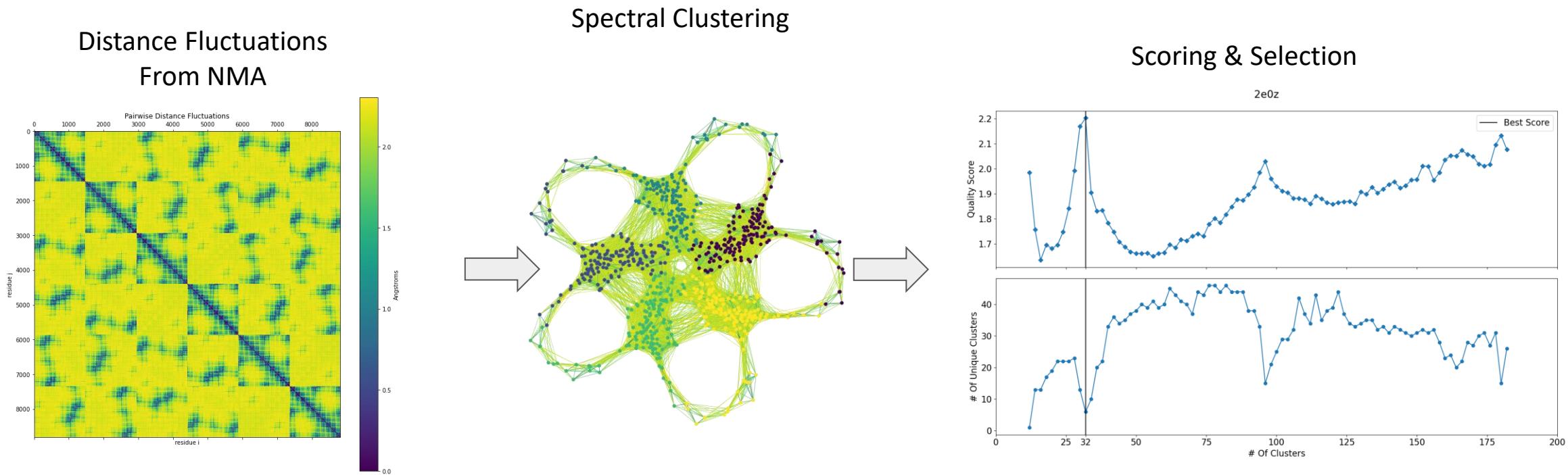
Atomic model



Elastic Network Model



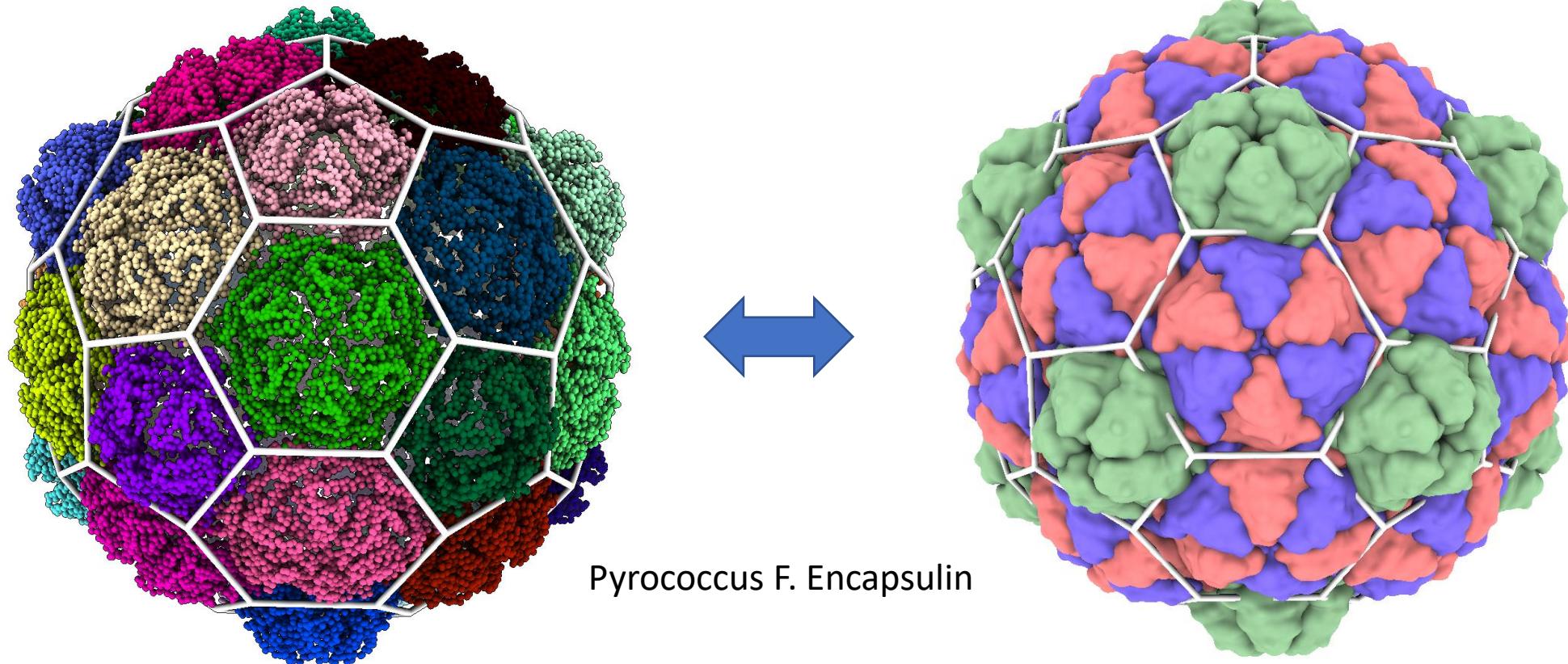
Step 2: Quasi-Rigid Domain Subdivision



$$f_{ij}^2 = \text{Var}(d_{ij}^2) = \langle d_{ij}^2 \rangle - \langle d_{ij} \rangle^2$$

Brown and Luque, In Preparation

Step 3: Geometrical Classification

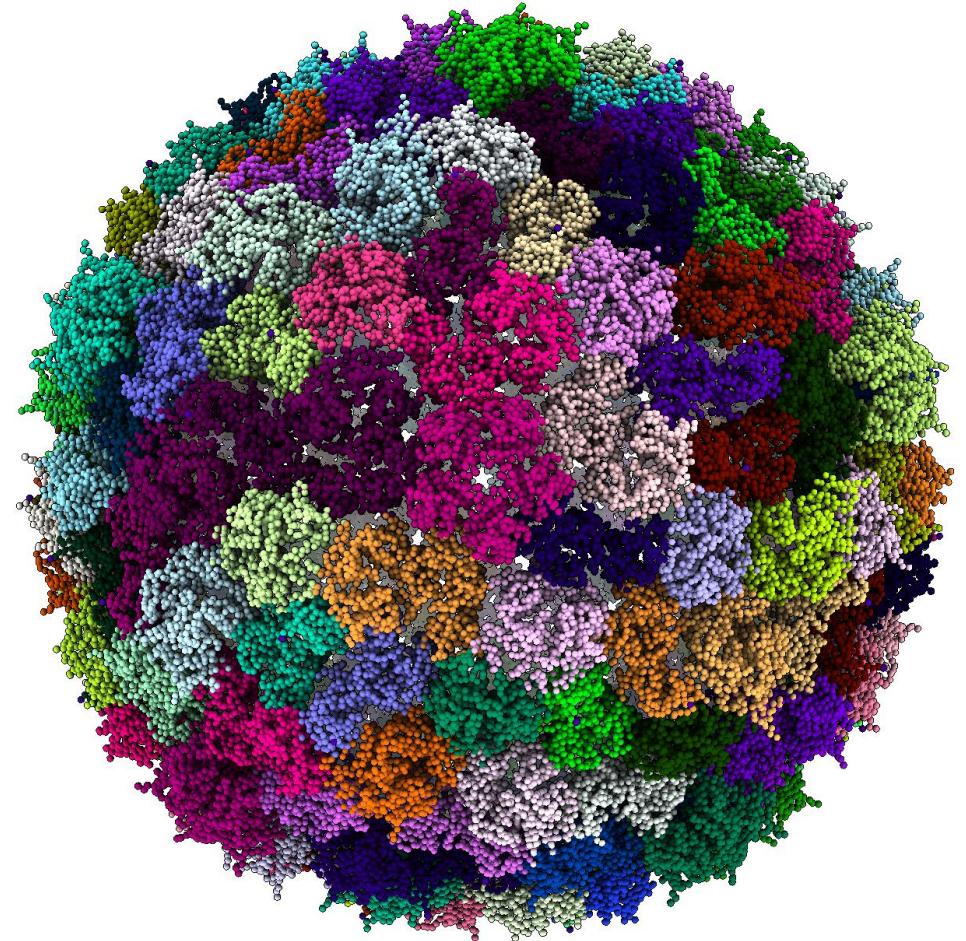
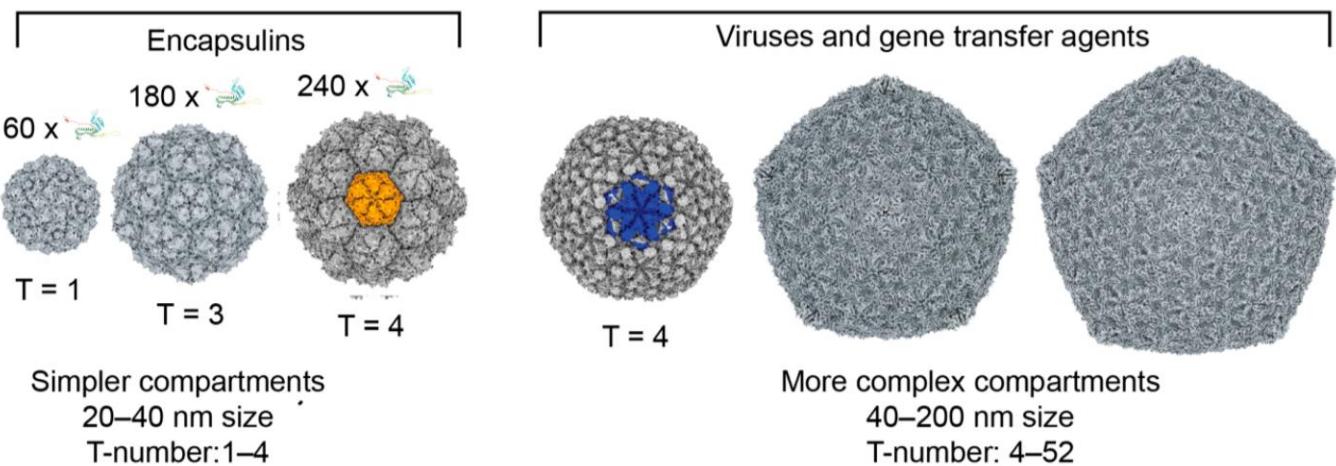


Pyrococcus F. Encapsulin

Brown and Luque, In Preparation

Results Summary

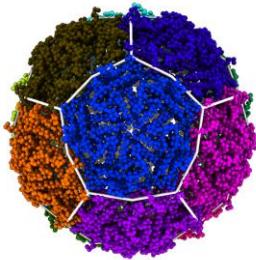
- 15 Total Structures
 - 7 Hexagonal
 - 4 Encapsulins
 - 2 Trihexagonal
 - 2 Trihexagonal-Dual
 - 4 Uneven Subdivisions (Inconclusive)



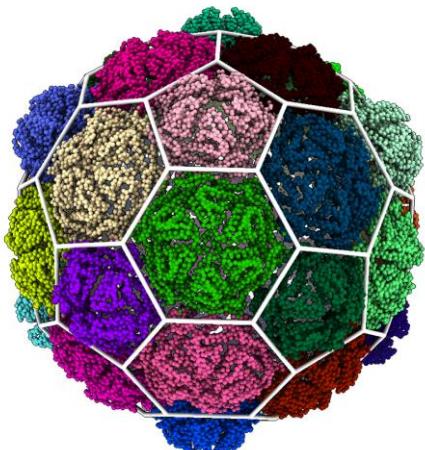
Phage 80-alpha - Uneven Subdivisions

Results – Hexagonal Structures

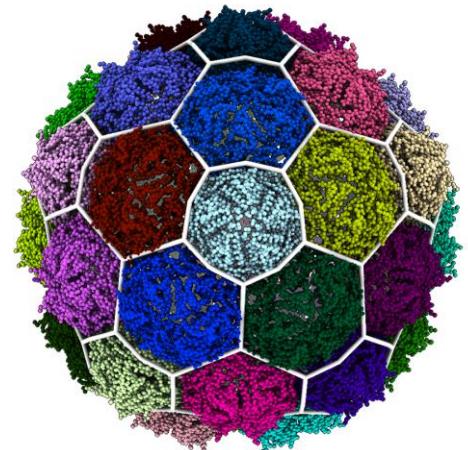
60 Proteins



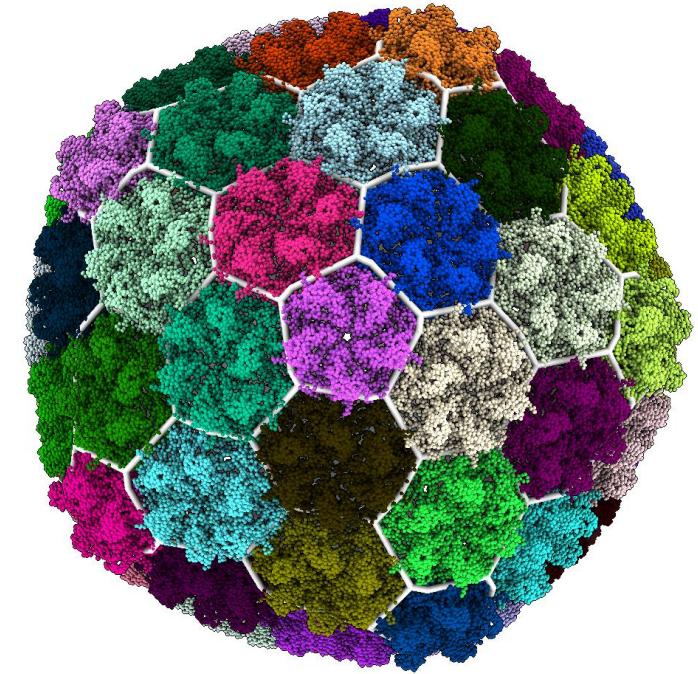
180 Proteins



240 Proteins



420 Proteins

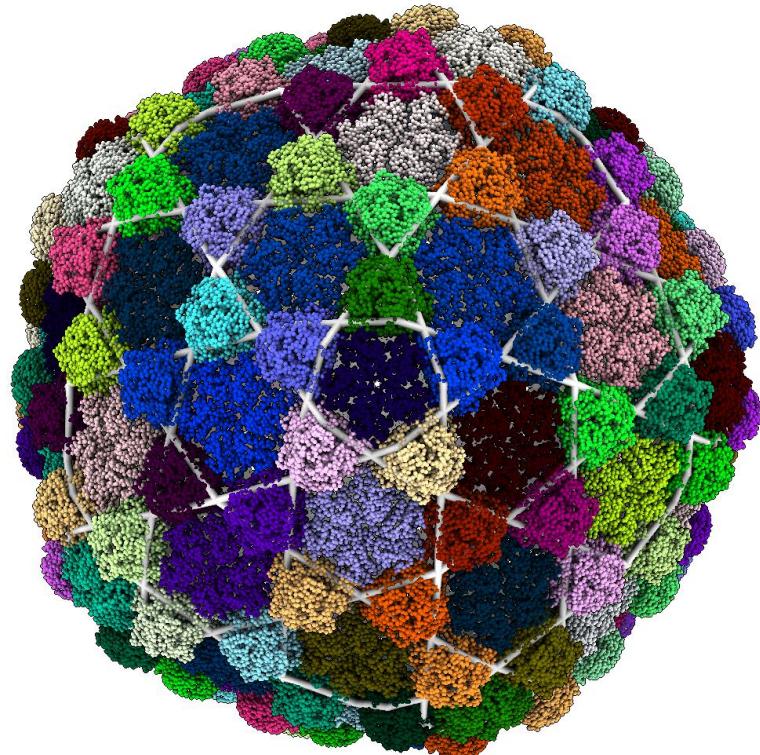


Encapsulins

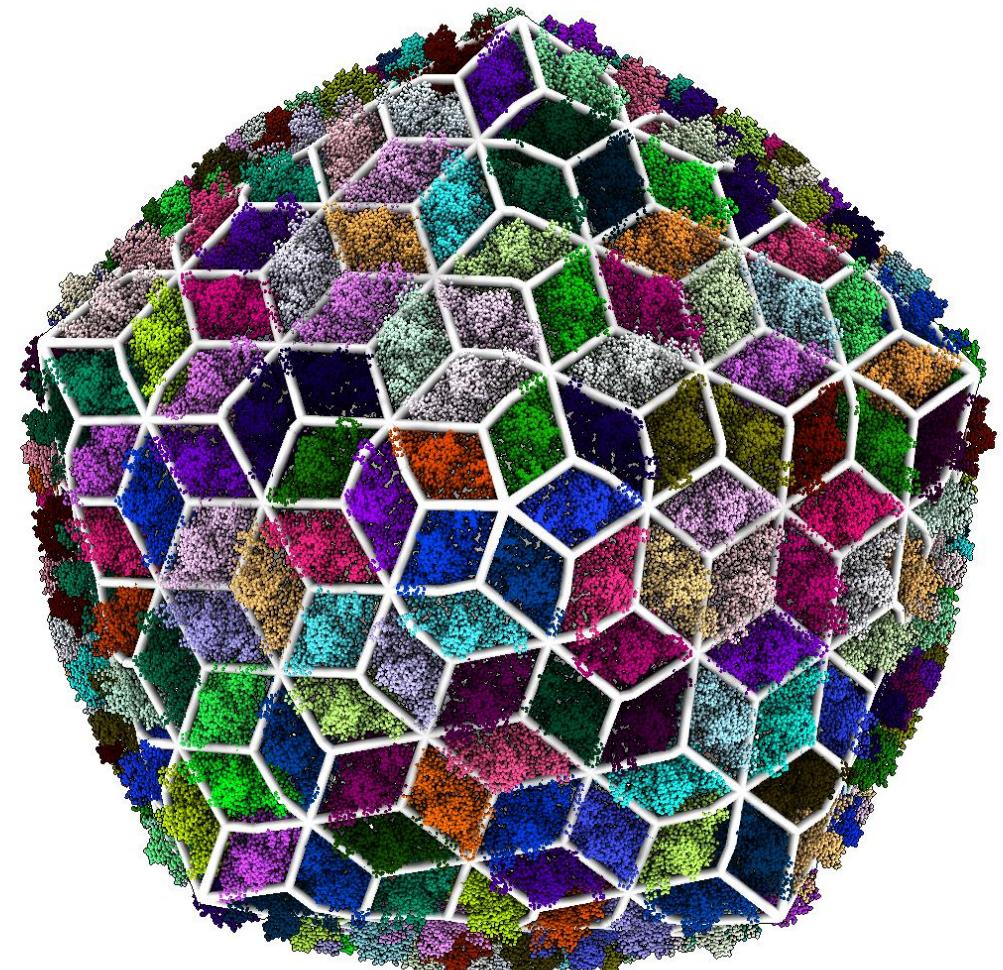
Brown and Luque In Preparation

Results – Reinforcement Proteins

420 Major Proteins
140 Reinforcement Proteins



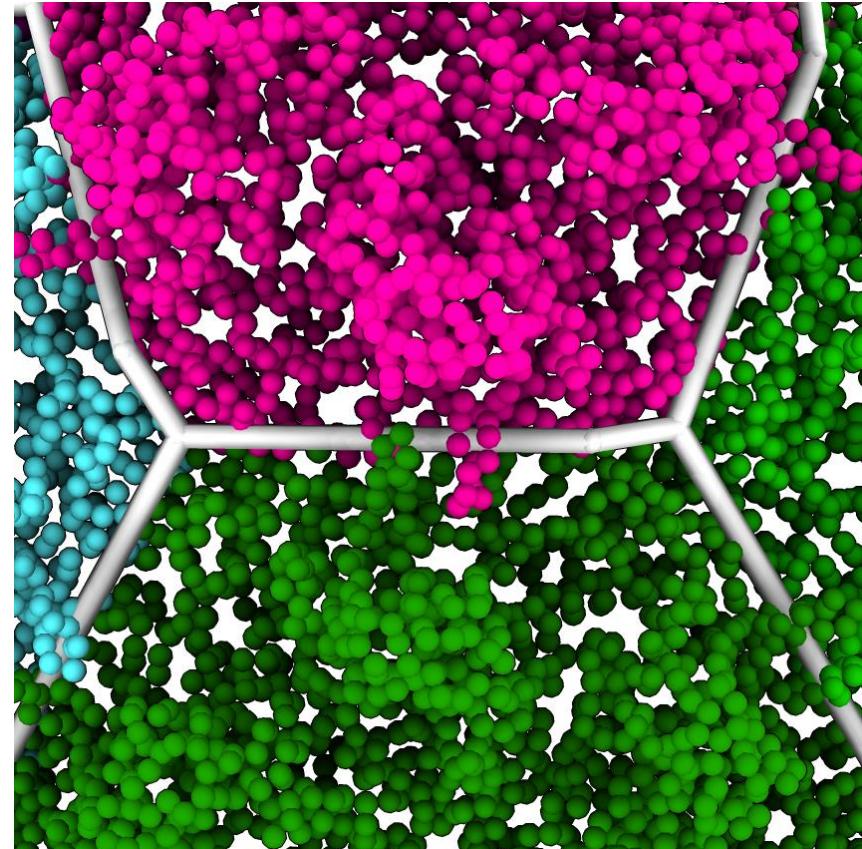
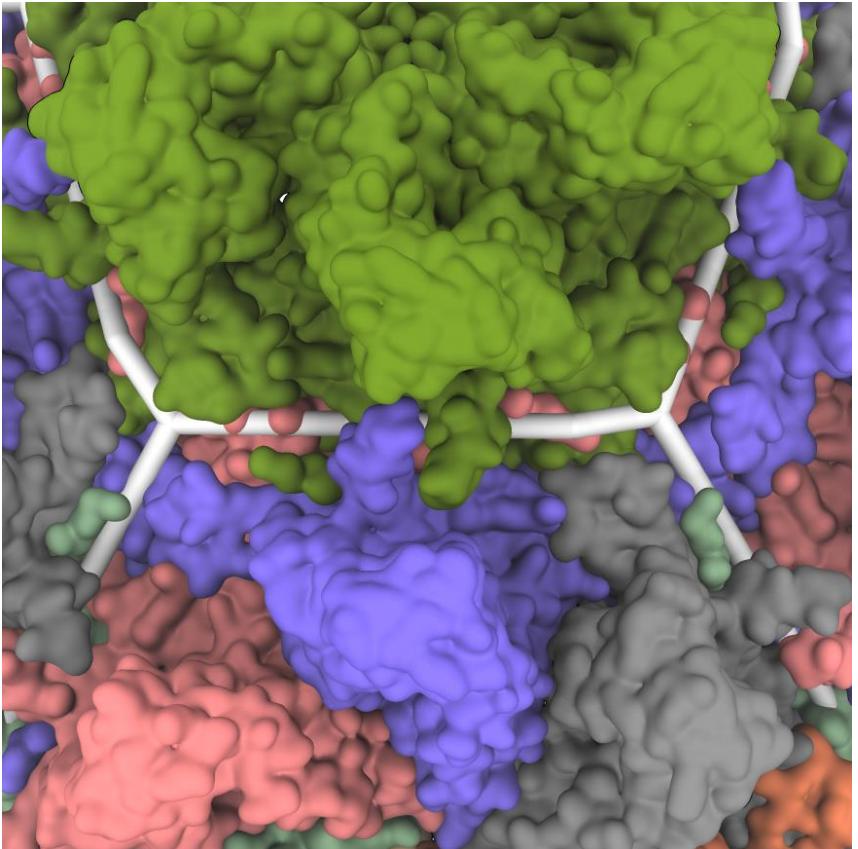
780 Major Proteins
260 Reinforcement Proteins



Brown and Luque In Preparation

Results - Crossing Domains

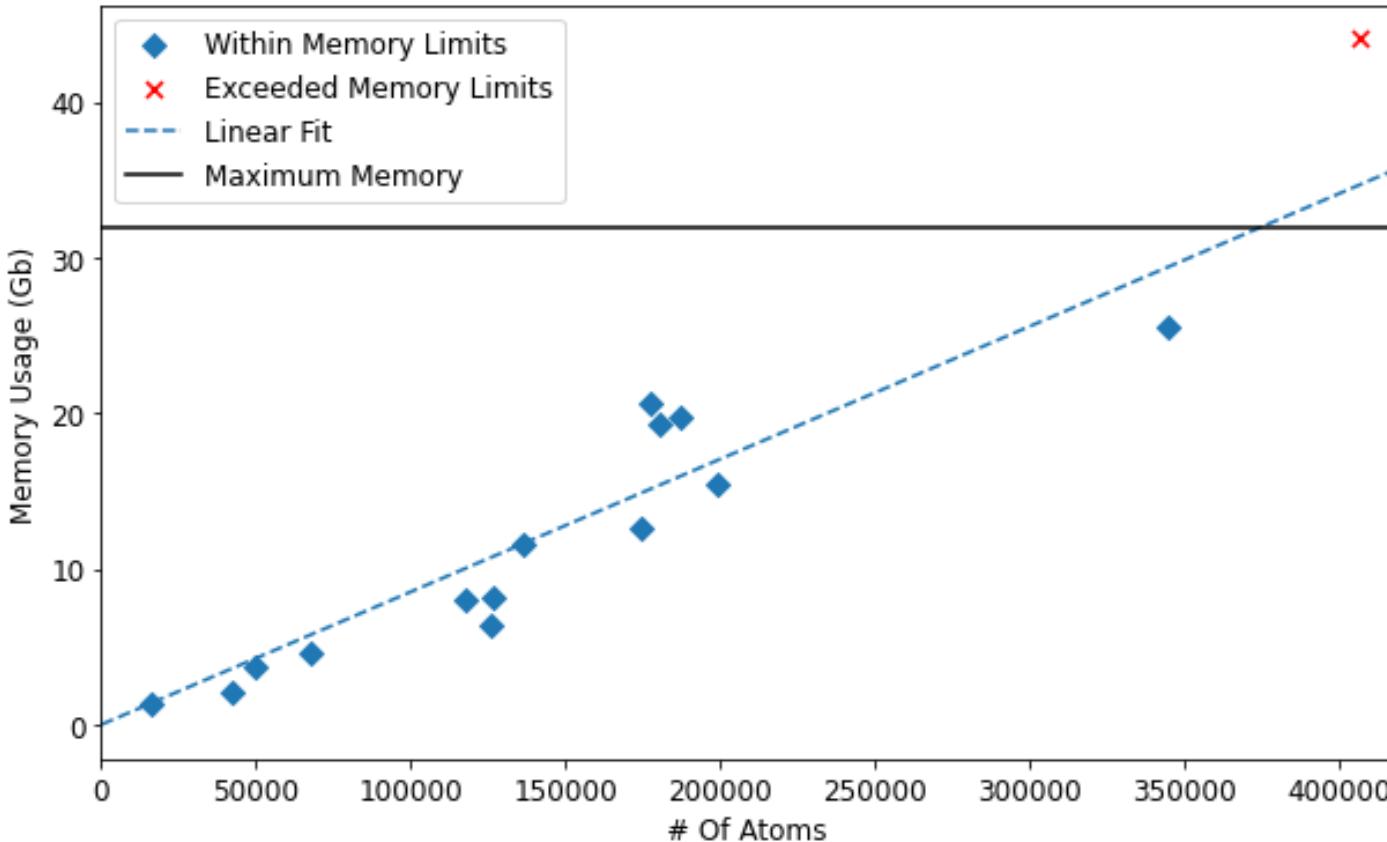
- Bacteriophage P22



Brown and Luque, In Preparation

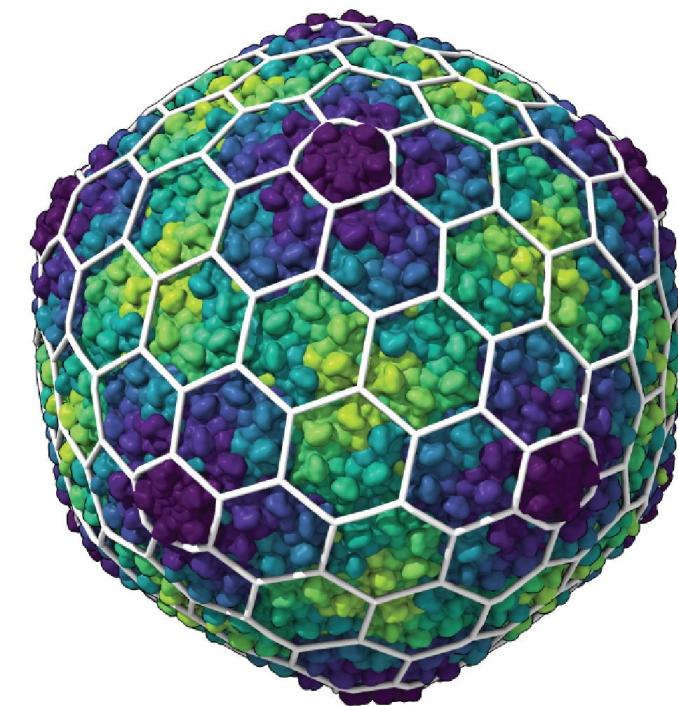
Memory Limitations

Memory Required For Normal Mode Analysis



Brown and Luque
In Preparation

Limit of 32 Gb \approx 380,000 Atoms



Isometric Phage T4
Exceeded Memory Requirements

Conclusion

- HK97-Fold
 - Hexagonal Structure
 - Reinforcement Proteins
 - Extended Domains
- Classification Method
 - Larger Capsids - Reduce Memory Requirements
 - Symmetry
 - Modularity
 - Physical Models
 - Clustering Algorithms

Acknowledgements

Luque Lab

- Antoni Luque
 - Diana Lee
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 - Aurora Vogal
 - Vaishnavi Patel
- Anuradha Agarwal
 - Meghan Osato



UC San Francisco

- ChimeraX Development Team
 - Tom Goddard



Grant # 1951678

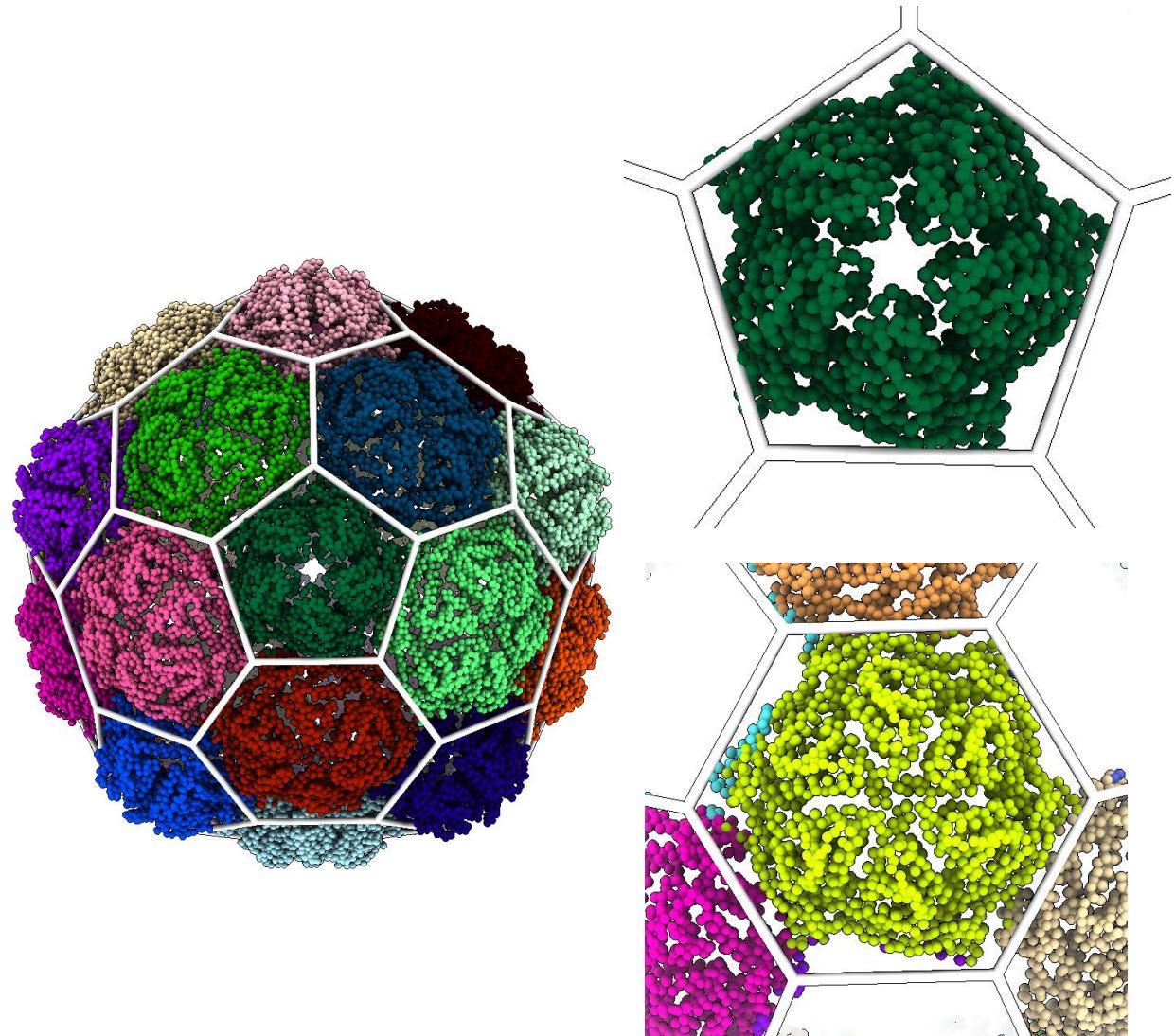
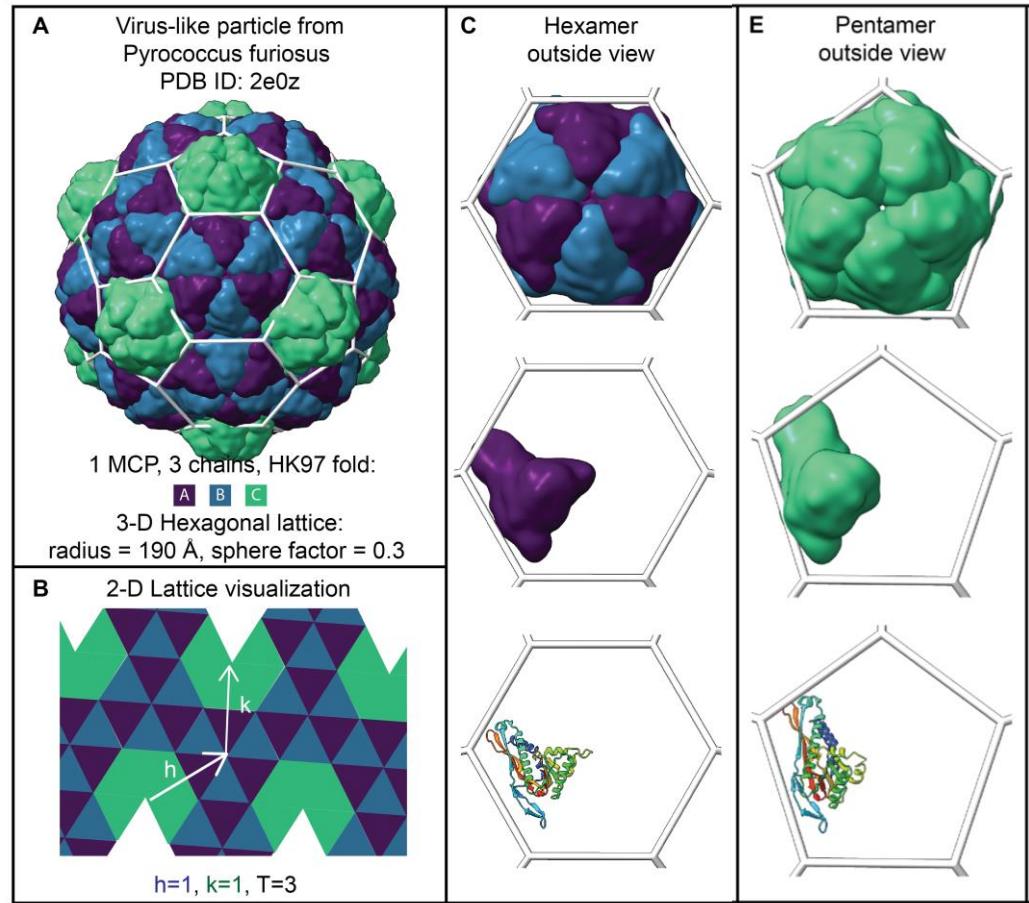
GORDON AND BETTY
MOORE
FOUNDATION

<https://doi.org/10.37807/GBMF9871>



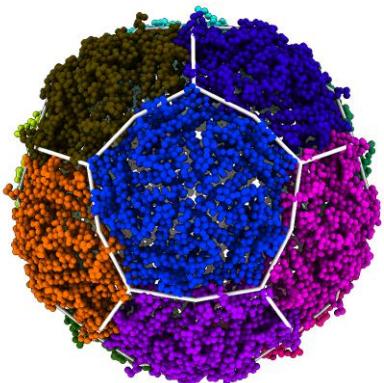
Questions

Results – Comparison With Geometric

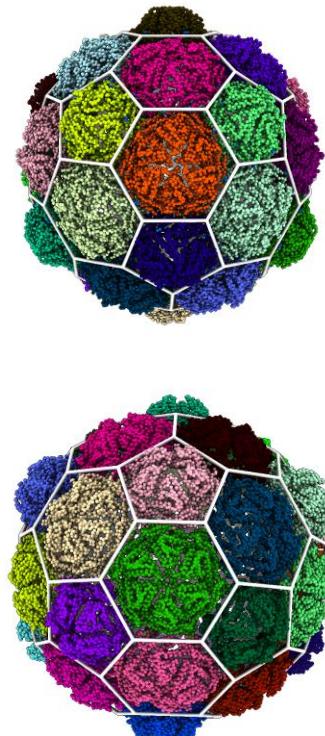


Results - Hexagonal

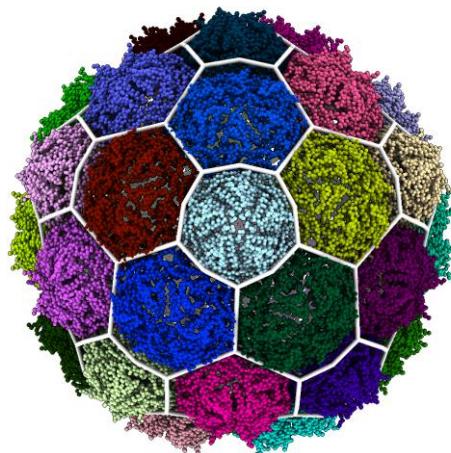
60 MCPs



180 MCPs



240 MCPs

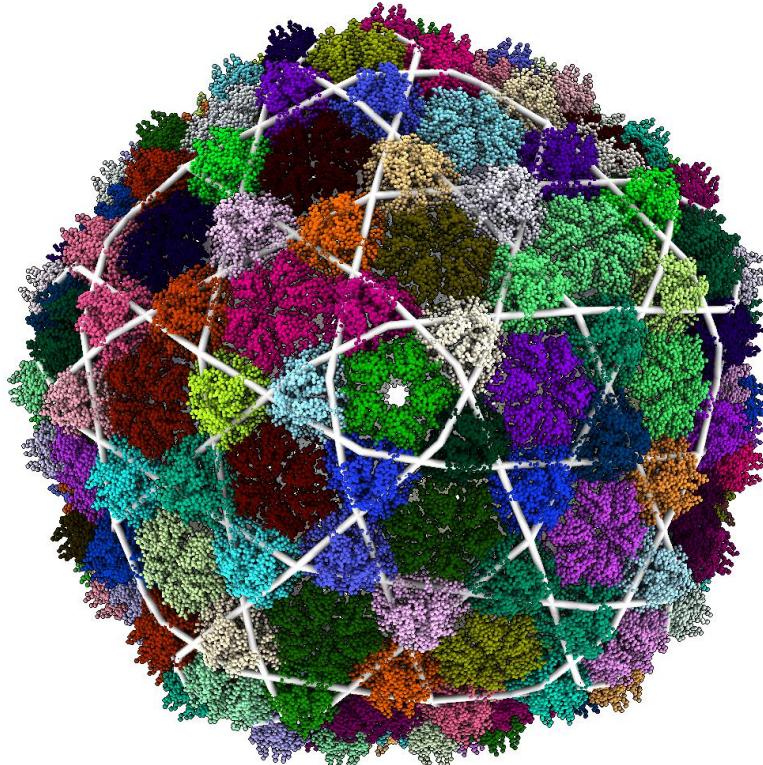
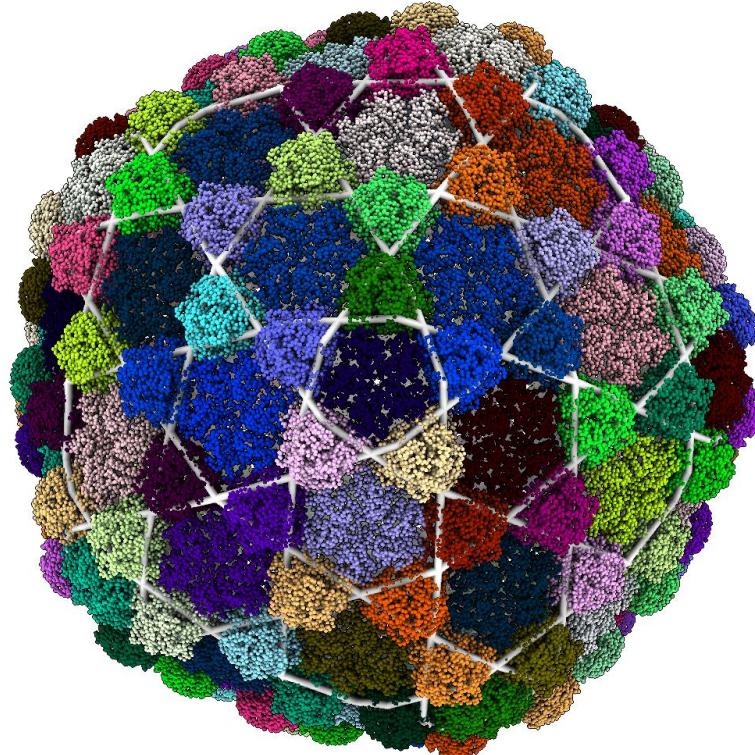


420 MCPs



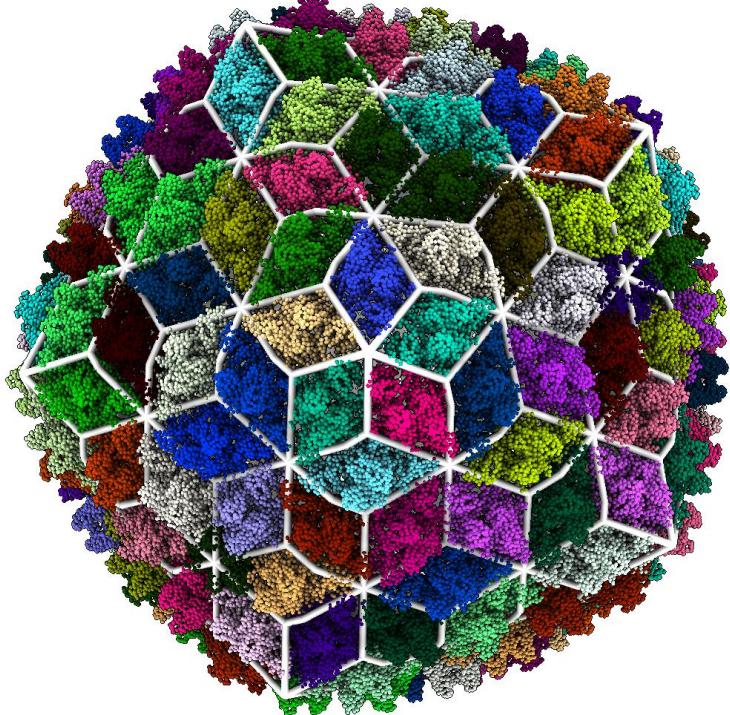
Results – Trihexagonal

420 MCPs & 140 Reinforcement Proteins

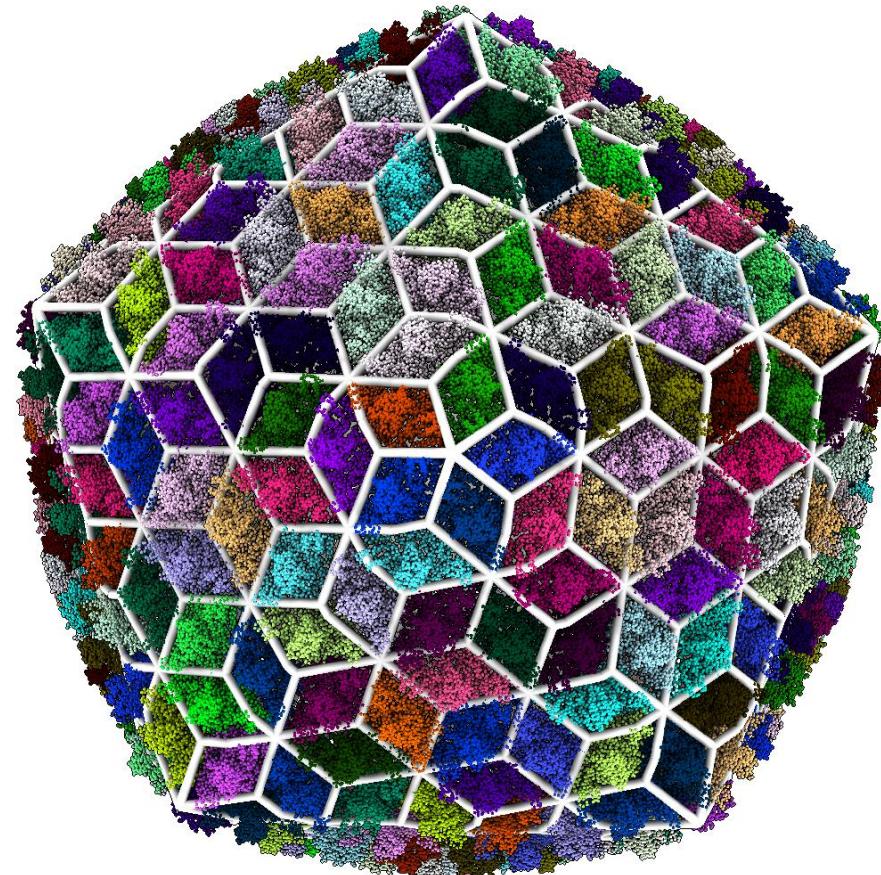


Results – Trihexagonal-Dual

420 MCPs & 140 Reinforcement Proteins

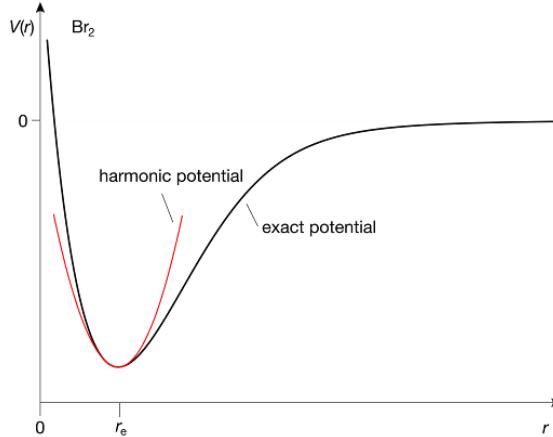


780 MCPs & 260 Reinforcement Proteins

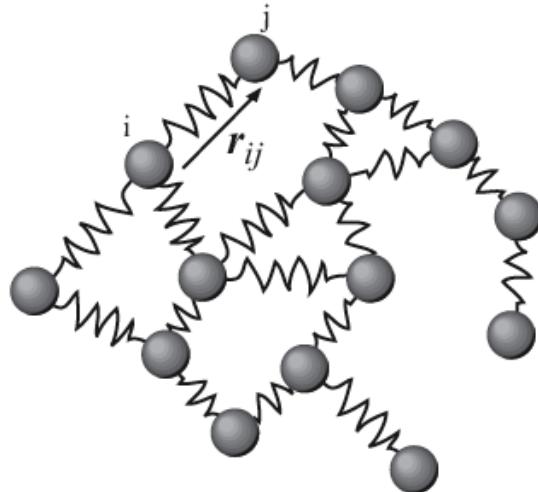


Model Assumptions & Limitations

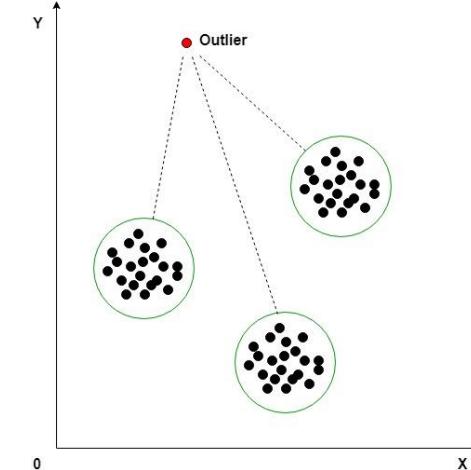
Harmonic Potentials



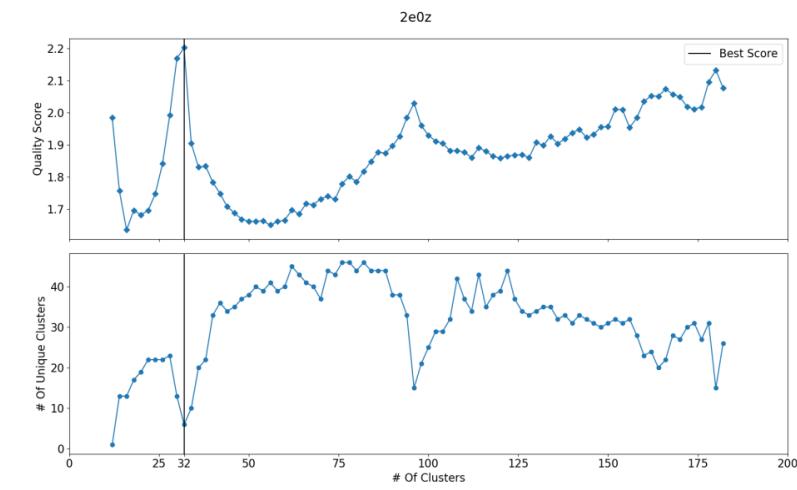
ENM
Coarse
Graining



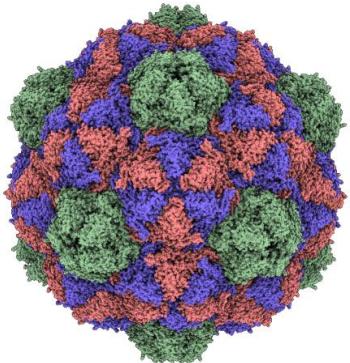
No Outlier Removal



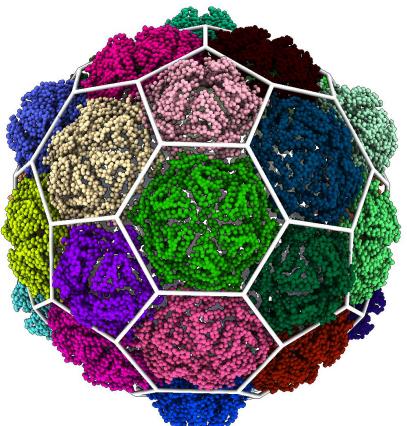
Subdivision
Selection



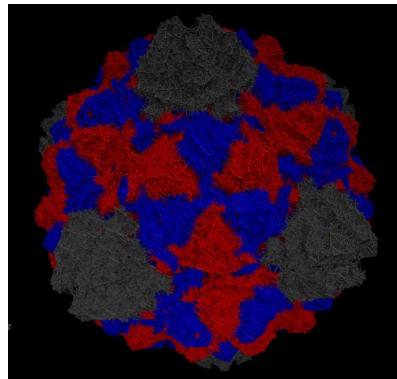
Atomic model



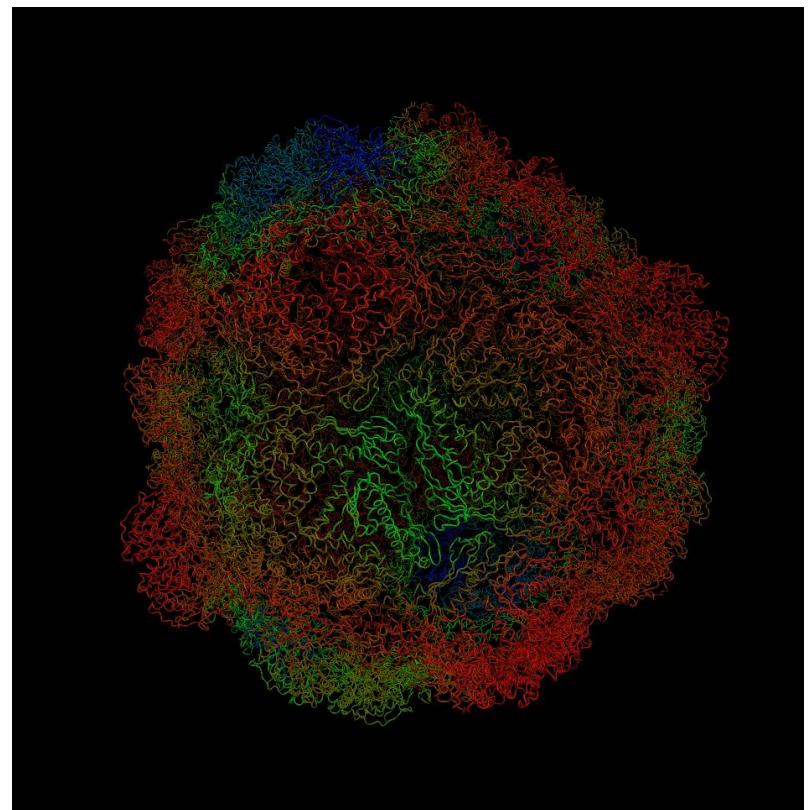
Icosahedral lattice assignment



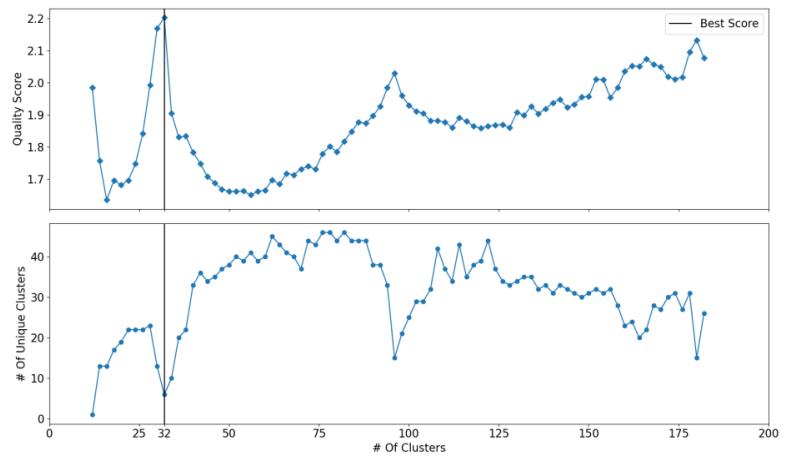
Elastic Network Model



Normal modes analysis



Scoring Subdivision



Performance

Constructing Hessian

$$\mathbf{H}_{ij} = -\frac{\gamma_{ij}}{(R_{ij}^0)^2} \begin{bmatrix} (x_{ij}^0)^2 & x_{ij}^0 y_{ij}^0 & x_{ij}^0 z_{ij}^0 \\ x_{ij}^0 y_{ij}^0 & (y_{ij}^0)^2 & y_{ij}^0 z_{ij}^0 \\ x_{ij}^0 z_{ij}^0 & y_{ij}^0 z_{ij}^0 & (z_{ij}^0)^2 \end{bmatrix}$$

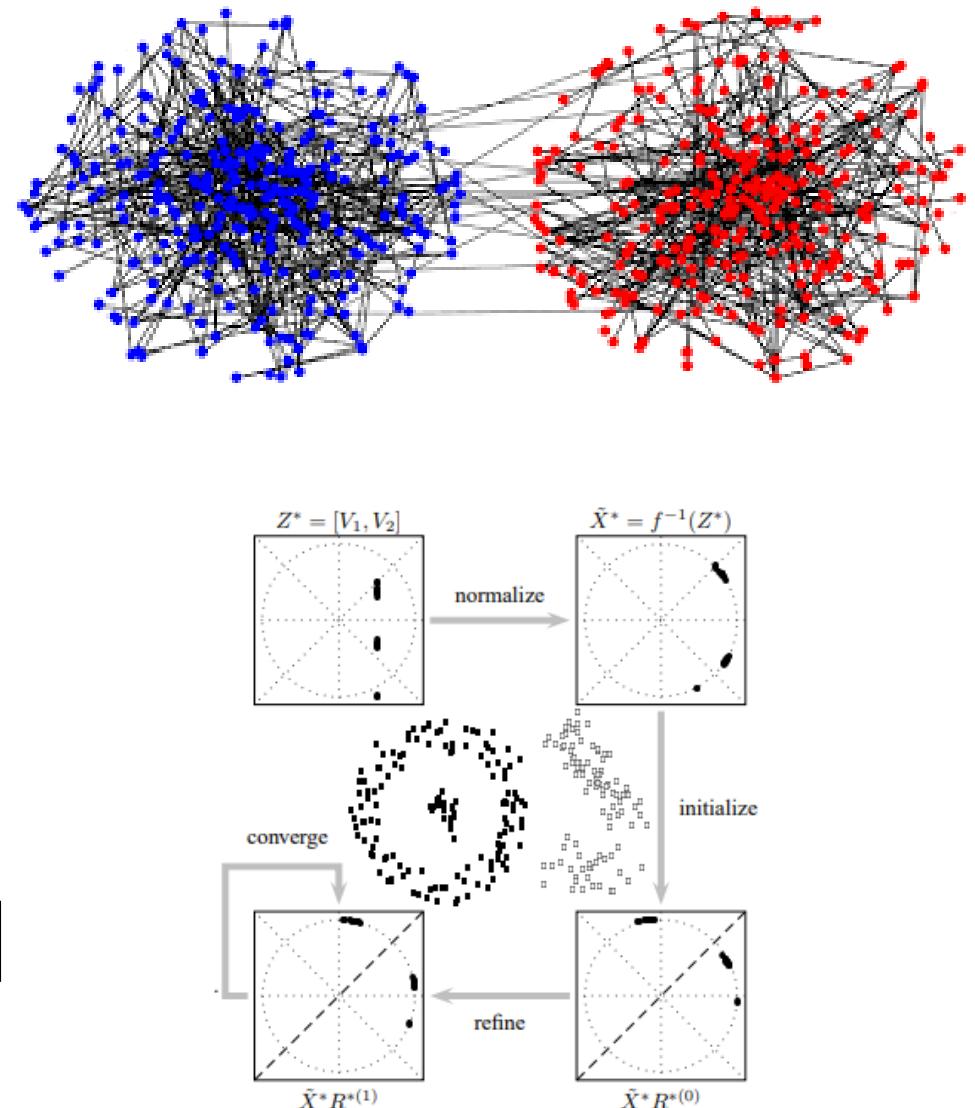
Calculate Normal Modes

$$\bar{H}^{-1} = \sum_{k=1}^{n_k} \frac{1}{\omega_k^2} v_k \otimes v_k$$

Of Modes

Eigenvectors/Normal Modes

Lowest Frequencies



Yu, Shi, IEEE 2003

Capsid	T #	Additional Proteins	Result
Th. Maritima	1	None	Hexagonal
Pyr. Furiosus	3	None	Hexagonal
Myx. Xanthus	3	None	Hexagonal
Quasi. Thermo.	4	None	Hexagonal
P22 Mature	7	None	Hexagonal
Phage Sf6	7	None	Hexagonal
Phage T7	7	None	Hexagonal
Bordetella	7	2-Fold Axis	Trihex-dual
Siphov. Mic1	7	2-Fold Axis	Trihex-dual
Siphov. TW1	7	3-Fold Axis	Trihexagonal
YSD1 Phage	7	3-Fold Axis	Trihexagonal
Siphov TW1	13	2-Fold Axis	Trihex-dual

Quasi-Rigid Domain Decomposition

- We implement the method described in (Ponzoni & Polles 2015) to identify quasi-rigid domains
 1. Represent the capsid using an Elastic Network Model (ENM)
 2. Apply Normal Mode Analysis to approximate the pairwise distance fluctuations between residues
 3. Use Spectral Clustering techniques to optimally divide the capsid into quasi-rigid domains
 4. Visualize the result and assign a geometric classification based on the clusters